IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **David John King**	Confirmation No.: **4275**
Serial No.: **10/731,759**	Group Art Unit: **1643**
Filing Date: **December 8, 2003**	Examiner: **Hong Sang**

For: **MONOVALENT ANTIBODY FRAGMENTS**

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APPEAL BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellants' appeal from the rejections of claims 11-16 set forth in a Final Office Action dated as mailed December 26, 2008. A Notice of Appeal with a response to this Final Office Action and a Petition to request a three-month extension of time was filed with the appropriate fees on June 26, 2009. An Advisory Action indicating that the amendments submitted June 26, 2009 would be entered issued on July 21, 2009. Appellants hereby request a five-month extension of time and authorize that the concomitant fee be charged to Deposit Account 50-3111. Appellants also authorize the charging of the appeal brief fee under 37 C.F.R. § 41.20(b)(2) to Deposit Account 50-3111.

1. REAL PARTY IN INTEREST

The real party in interest is Celltech R&D Limited.

2. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any other appeals or interferences, which will directly affect, be directly affected by, or have a bearing on the Board's decision in the present appeal.

3. STATUS OF CLAIMS

The claims pending in this application are Claims 11-16. Claims 11-16 stand rejected and are on appeal. Claims 1-10 were cancelled. The claims are appended hereto in a Claims Appendix.

4. STATUS OF AMENDMENTS

On June 26, 2009, Appellants submitted a response to the Final Office Action issued December 26, 2008 including minor amendments to the claims. An Advisory Action issued on July 21, 2009 indicating that the claim amendments set forth in the June 26, 2009 response would be entered, but that the Claims stood rejected.

5. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 11 provides a modified monovalent antibody fragment comprising a heavy chain and a light chain, wherein: said heavy chain consists of a V_H domain covalently linked at its C-terminus to a C_H1 domain; said light chain consists of a V_L domain, which is complementary to the V_H domain, covalently linked at its C-terminus to a C_L domain; said CH1 domain is extended to provide a hinge domain which contains only one cysteine residue; the cysteine residues in the V_H, C_H1, V_L and C_L domains are in disulphide linkage to each other; and the cysteine residue in the hinge domain is covalently linked through its sulphur atom to a polymer molecule, wherein said polymer molecule has an average molecular weight of from about 25,000 Da to about 40,000 Da.

Support for claim 11 may be found *inter alia* in the specification as originally filed at page 3, line 35 to page 4, line 3; page 4, line 25 to page 6, line 10; and page 6, line 34 to page 7, line 8.

Claim 12 provides an antibody fragment according to claim 11, wherein the polymer is an optionally substituted, straight or branched chain polyalkylene, polyalkenylene or polyoxyalkylene polymer, or a branched or unbranched polysaccharide, said polymer being optionally substituted with hydroxy, methyl, or methoxy groups.

Support for claim 12 may be found *inter alia* in the specification as originally filed at page 6, lines 12-20.

Claim 13 provides an antibody fragment according to claim 12, wherein the polymer is an optionally substituted, straight or branched chain poly(ethylene glycol), poly(propylene glycol) or poly(vinyl alcohol) or a derivative thereof reactive for linking the antibody fragment and polymer, said polymer being optionally substituted with hydroxy, methyl, or methoxy groups.

Support for claim 13 may be found *inter alia* in the specification as originally filed at page 6, lines 18-23.

Claim 14 provides an antibody fragment according to claim 13 wherein the polymer is methoxy(polyethylene glycol), or a derivative thereof reactive for linking the antibody fragment and polymer.

Support for claim 14 may be found *inter alia* in the specification as originally filed at page 6, line 24.

Claim 15 provides an antibody fragment according to claim 11 covalently attached to one or more effector or reporter molecules.

Support for claim 15 may be found *inter alia* in the specification as originally filed at page 4, lines 3-5.

Claim 16 provides a pharmaceutical composition comprising a monovalent antibody fragment according to any one of the preceding claims together with one or more pharmaceutically acceptable excipients, diluents or carriers.

Support for claim 16 can be found in the specification as filed, *inter alia,* at page 11, line33 to page 12, line 5.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There is one issue to be resolved in this appeal: whether Zapata et al., FASEB J. 1995. 9:A1479 (herein "Zapata") in view of Griffiths et al., U.S. Patent 5,670,132 (herein "Griffiths") render claims 11-16 obvious.

7. ARGUMENT

Claims 11-16 Are Not Obvious Over Zapata In View Of Griffiths

Claims 11-16 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Zapata in view of Griffiths.

The Office argues that Zapata discloses an Fab fragment which contains a single cysteine in the hinge region including coupling of monomethoxypoly(ethylene glycol) to the cysteine. The Office acknowledges that Zapata fails to disclose a polymer of 25,000 to about 40,000 Da as recited in Claim 11, or fragment with an effector or reporter molecule as recited in Claim 15, or a pharmaceutical composition with a carrier as recited in Claim 16. Accordingly, the Office alleges that the teachings of Griffiths make up these deficiencies.

The Office alleges that Griffiths teaches site specific conjugation of PEG to Fab or Fab' outside the variable region, wherein the molecular weight of the PEG can be 30,000 Da. The Office cites MPEP § 2144.05 which states that in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. MPEP § 2144.05 cites *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). The Office further alleges that Griffiths teaches an antibody conjugated to 1-10 PEG moieties of 5,000 Da, to reduce renal uptake and retention of the PEGylated antibody fragment after radiolabelling.

Appellants respectfully disagree with the Office's interpretation of the teachings of Griffiths.

Griffiths does not disclose a PEG having a molecular weight of 30,000 Da. Instead, Griffiths discloses a range of suitable molecular weight of 1,000-30,000 Da for PEGS (See col. 3, lines 12-15 as cited by the Office). Griffiths does not contemplate the use of any PEGS of a molecular weight higher than 30,000 Da, as recited in Claim 11.

Appellants maintain that according to M.P.E.P. §2131.03, when a prior art reference discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, and the reference teaches a broad range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. "[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." *Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 1000, 78 USPQ2d 1417, 1424 (Fed. Cir. 2006). In this case, the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, the court remarked that while there was a slight overlap between the reference's preferred range and the claimed range, that overlap was not sufficient for anticipation.

Similarly, Appellants maintain that although there is a slight overlap of the range disclosed in Griffiths and the claimed range as recited in Claim 11, this is not a sufficient disclosure in itself to anticipate the claimed range, and therefore Griffiths cannot be cited as a prior art reference as teaching the claimed range. Griffiths does not contemplate any PEGS of a molecular weight *higher* than 30,000 Da, while the claimed invention does not contemplate any PEGS of a molecular weight *lower* than 25,000 Da. The slight overlap between this range and that which is claimed is minor when taking in consideration the broad range disclosed by Griffiths, namely 1,000 to 30,000 Da, and cannot be construed to provide a teaching of the claimed range, namely 25,000 to about 40,000 Da.

In addition, Griffiths discloses the use of 1-10 5,000 Da PEGS, not the attachment of **one** PEG of a molecular weight ranging from 5,000-50,000 Da. In characterizing this disclosure, the Office has incorrectly interpreted this as teaching the attachment of a **single** PEG moiety of 5,000 to 50,000 Da. The Office's interpretation is patently incorrect. Claim 11 recites, in relevant part, that the "CH1 domain is extended to provide a hinge domain which contains **only one** cysteine residue" (Emphasis added). This limitation is not disclosed in Griffiths. One

skilled in the art would understand Griffiths as disclosing the use of multiple PEG moieties which necessarily requires *more than one* cysteine residue. The disclosure of Griffiths does not allow for "only one" cysteine in the hinge region to which a single PEG of molecular weight 25,000 to 40,000 Da is attached, but rather to multiple PEGS of molecular weight 5,000 to 50,000 Da attached to multiple cysteines.

Furthermore, Appellants note that the Griffiths discusses site-specific PEGylation on thiol groups using **intact** immunoglobulins as opposed to monovalent antibody fragments as claimed (col. 3, l. 62, to col. 4, l. 12). This is because, as discussed in more detail below, Griffiths teaches attaching radiolabels to the hinge regions cysteines, not a polymer. One skilled in the art certainly would not have been led to combine Zapata and Griffiths, and certainly would not have arrived at the claimed invention by combining these teachings.

Finally, Appellants maintain that, because Griffiths teaches attaching radiolabels to the hinge region cysteines, Griffiths actually teaches away from the claimed invention. Although the Office acknowledges that the hinge region cysteines in Griffiths are radiolabelled, it alleges that this is not the only site for linking the radioisotope (Final Office Action, page 4). This, however, is the only site disclosed in Griffiths. The Office is disregarding the specific teachings of the reference; this is error.

Griffiths discusses producing free thiol groups for direct labeling of divalent antibody fragments **already** derivatized with PEG with the radiolabel, i.e., Tc-99m. Griffiths further discusses that the disulphide bonds in the hinge region of such divalent antibody fragments are generally more accessible to reducing agents and can, thus, be selectively cleaved under the proper conditions (col. 4, ll. 55-60.). Accordingly, Griffiths specifically describes attaching the radiolabel to a *hinge region* thiol, i.e., a cysteine.

As stated above, Claim 11 recites that the fragment comprises a hinge region with a **single** cysteine, to which the polymer, e.g., PEG, is attached. Griffiths teaches that the radiolabel is to be attached to a hinge region cysteine of an already PEG-derivatized antibody fragment. Thus, if a single cysteine is present in the hinge region of the fragment, it is to be radiolabelled, not pegylated, according to Griffiths. The Office attempts to dismiss the teaching away argument by stating that Griffiths is a secondary reference merely used to show that PEG with a wide variety of average molecular weight can be linked to an antibody (Advisory Action, p. 2).

No case law is cited in support. In fact, the case law is to the contrary. A prior art reference must be considered in its entirety, i.e., as a **whole**, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Accordingly, Griffiths teaches away from a fragment having a single hinge region cysteine to which a polymer is attached as is presently claimed.

For the foregoing reasons, Appellants request that this rejection be withdrawn and Claims 11-16 allowed.

8. CLAIMS APPENDIX

A Claims Appendix containing a copy of the claims involved in the appeal is attached.

9. EVIDENCE APPENDIX

No Evidence Appendix is attached.

10. RELATED PROCEEDINGS APPENDIX

No Related Proceedings Appendix is attached.

Respectfully submitted,

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CLAIMS APPENDIX

11. A modified monovalent antibody fragment comprising a heavy chain and a light chain, wherein:

said heavy chain consists of a V_H domain covalently linked at its C-terminus to a C_H1 domain; said light chain consists of a V_L domain, which is complementary to the V_H domain, covalently linked at its C-terminus to a C_L domain;

said CH1 domain is extended to provide a hinge domain which contains only one cysteine residue; the cysteine residues in the V_H, C_H1, V_L and C_L domains are in disulphide linkage to each other; and the cysteine residue in the hinge domain is covalently linked through its sulphur atom to a polymer molecule, wherein said polymer molecule has an average molecular weight of from about 25,000 Da to about 40,000 Da.

12. The antibody fragment according to claim 11 wherein the polymer is an optionally substituted, straight or branched chain polyalkylene, polyalkenylene or polyoxyalkylene polymer, or a branched or unbranched polysaccharide, said polymer being optionally substituted with hydroxy, methyl, or methoxy groups.

13. The antibody fragment according to claim 12 wherein the polymer is an optionally substituted, straight or branched chain poly(ethylene glycol), poly(propylene glycol) or poly(vinyl alcohol) or a derivative thereof reactive for linking the antibody fragment and polymer, said polymer being optionally substituted with hydroxy, methyl, or methoxy groups.

14. The antibody fragment according to claim 13 wherein the polymer is methoxy(polyethylene glycol), or a derivative thereof reactive for linking the antibody fragment and polymer.

15. The antibody fragment according to claim 11 covalently attached to one or more effector or reporter molecules.

16. A pharmaceutical composition comprising a monovalent antibody fragment according to any one of the preceding claims together with one or more pharmaceutically acceptable excipients, diluents or carriers.